REMARKS

Claims 1-40 are pending in the application. The Examiner has withdrawn claims 5 and 23-40. Claims 1-4 and 6-22 are rejected. Claims 1, 9, and 16 are presently amended. Applicants submit herewith a Declaration of Gilbert R. Gonzales and Paolo Manfredi under 37 C.F.R. § 1.132 ("Declaration"). In view of the amendments, the Declaration, and the discussion below, it is submitted that the application is in condition for allowance.

Claim Rejections 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-4 and 6-22 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,586,478 (Ackman) in view of U.S. Patent No. 6,264,981 (Zhang). The Examiner states that Ackman teaches compositions for improving sleep, which include methadone, and Zhang teaches a transmucosal drug dosage form (e.g., a lollipop) with improved oral mucosal delivery of a pharmaceutical agent. The Examiner then suggests that it would have been obvious to one of ordinary skill in the art to use the drug dosage form of Zhang to deliver the composition of Ackman, thereby delivering the sleep-promoting composition including methadone transmucosally. In view of the claims as presently amended, Applicants respectfully disagree.

Applicants first note that each of independent claims 1, 9, and 16 have been amended to recite that the dosage formulation of the composition is "nonsedative,

analgesic dosage formulation effective to treat acute pain." Thus, all of the claims of the present application are directed to, and recite, a composition including methadone for the treatment of acute pain, which is nonsedative. Support for this amendment may be found at least at page 2, lines 3-7; page 3, lines 13-15; page 9, line 23 through page 10, line 5; page 10, lines 5-7; and page 20, lines 19-21. There, the application describes that when opioids are used to treat pain, patients generally become tolerant to the analgesic effects of the opioid and thus require escalation in dosage amounts in order to maintain the desired analgesic effects. This results in increased side effects, one of which is sedation. However, tolerance to the analgesic effects of methadone develops more slowly than with other commonly used opioids. And so, the invention of the present application is a composition including methadone that is nonsedative and can be used to combat sedative effects that may be found in other compositions. Further, the application describes that the presently claimed composition can be used to treat acute pain, such as breakthrough pain.

Applicants submit that neither Ackman, Zhang, nor their combination would cause one skilled in the art to conclude that methadone can be delivered transmucosally in a nonsedative composition for the treatment of patients with acute pain. Ackman discloses a pharmaceutical composition for improving sleep. The composition of Ackman includes a nitric oxide mimetic and an established drug for sleep disorders. Applicants submit that one skilled in the art would not look to Ackman for a

nonsedative composition including methadone (as is disclosed and claimed by the present application), due to Ackman explicitly describing a composition having sedative properties. As opposed to Ackman, when the composition including methadone of the present application is used for pain treatment, sedation is reduced. (See Declaration, paragraph 11). Thus, a dosage form including methadone for the treatment of sleep disorders (as described by Ackman) would not be a viable nonsedative treatment option, as is the presently claimed invention. (See Declaration, paragraph 11).

Further, Ackman lists several possible drugs as "established drugs for sleep disorders," including methadone (see at least at column 4, lines 21-32). Applicants submit that the characterization of methadone as an established drug for sleep disorders is erroneous. (See Declaration, paragraph 12). To the contrary, methadone has never been approved for the treatment of sleep disorders. (See Declaration, paragraph 12). Thus, the disclosure of a methadone/nitric oxide-mimetic dosage form by Ackman, including the erroneous statement that methadone is a "well established drug for sleep disorders," would further steer one skilled in the art away from Ackman, because one skilled in the art would consider the overall teaching of Ackman to be fallacious. (See Declaration, paragraph 12).

Zhang discloses a transmucosal dosage form including opioid agonists such as fentanyl, alfentanil, sufentanil, lofentanil, and carfentanil. However, Zhang does not disclose methadone. Applicants submit that methadone is not disclosed because

Zhang did not, and others skilled in the art would not, contemplate that methadone could be effective to treat acute pain.

More specifically, the opioid agonists disclosed by Zhang have a very short half-life and are very short acting (measured in minutes to less than an hour), are very potent (and so are used in microgram amounts), and are pure mu opioid agonists (i.e., they bind to the mu opioid receptors and have no other known analgesic property). (See Declaration, paragraph 14). Further, the drugs specifically disclosed by Zhang are synthetic opioids in the chemical structure group called anililidopiperidines. (See Declaration, paragraph 14). Methadone, however, is of a very different chemical structure group called diphenylpropylamines. (See Declaration, paragraph 14). Further, methadone has a very long half-life (up to several days) and has long-acting analgesic action, and it is much less potent (used in milligrams rather than micrograms). (See Declaration, paragraph 14). The characteristics of the drugs disclosed by Zhang are therefore very different and in some ways opposite from the characteristics of methadone. (See Declaration, paragraph 14). Due to these characteristics of methadone, one skilled in the art would not think that such a long-acting and less potent drug can be used for acute pain. (See Declaration, paragraph 14). In other words, the use of methadone as a drug for acute pain is antithetical to the use of, and prevailing conventional wisdom regarding, methadone, as would be known to a person skilled in the art. (See Declaration, paragraph 14).

Further, Applicants submit that methadone has unique pharmacodynamics well beyond opioid-like actions. For example, methadone is also an NMDA antagonist and a catecholamine re-uptake inhibitor, (both of these effects are analgesic), and therefore methadone is a unique drug that is not disclosed by mentioning the opioid family alone. (See Declaration, paragraph 15). Furthermore, as described above, the main mode of action of the drugs disclosed by Zhang is activation of the mu opioid receptor. These drugs do not work when the mu receptor is absent. (See Declaration, paragraph 15). To the contrary, methadone works very well as an analgesic in mice that are knockouts for the mu receptor gene, implying a different mode of analgesic action. (See Declaration, paragraph 15). Applicants submit that it is therefore not surprising that Zhang did not disclose methadone because Zhang and others skilled in the art would not believe that methadone would work in treating and/or alleviating acute pain. (See Declaration, paragraph 15).

In summary, Applicants submit that one skilled in the art would not consider a reference that teaches a sedative composition including methadone (Ackman) and a reference that specifically does not teach methadone for treating acute pain (Zhang) to reach the presently claimed nonsedative composition that includes methadone for treating acute pain.

In view of the above, Applicants request withdrawal of the rejection of claims 1-4 and 6-22 under 35 U.S.C. §103(a) as unpatentable over Ackman in view of Zhang.

Conclusion

For the foregoing reasons, it is submitted that all claims are patentable, and a Notice of Allowance is respectfully requested.

No fee is believed due. Any deficiencies or credits necessary to complete this communication should be applied to Deposit Account No. 23-3000.

The Examiner is invited to contact the undersigned attorney with any questions or remaining issues.

Respectfully submitted,
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